REMARKS

Claims 1-25 were pending in the application. Claims 1, 4, 5, 7, 10, 22 and 24 have been amended, claims 2, 3, 6, 8, 9, 11-21, 23 and 25 have been cancelled without prejudice. New claims 26-38 have been added. Accordingly, following entry of the amendments presented herein, claims 1-38 will be pending.

Support for the amendment to claim 1 and new claims 26-38 may be found throughout the specification. In particular, support for the limitation "amplifying exon 2 and 3 under conditions suitable to obtain an amplified product" may be found, for example, at page 12, lines 3-12.

No new matter has been added. The claim amendments and cancellations made herein should be in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election

Applicants elect group I (1-17 and 22-25) drawn to methods and primers for amplifying exon 2, 3 and/or 4 of HLA-A.

Objection to claim 4

Claim 4 has been objected to for failing to be in proper grammatical form. Accordingly, Applicant has amended claim 4 to correct this error in accordance with MPEP 608.01(m).

Rejection of Claims 1-9, 12, 15-17, and 22-25 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-9 and 22 under 35 U.S.C. §112, second paragraph, as being "incomplete for omitting essential steps, such omission amounting to

a gap between the steps." In particular, the Examiner is of the opinion that the "claims do not set forth the steps by which the hybridized primer is extended so as to result in the amplification of exon 2, 3 or 4 of HLA-A."

In response, Applicants have amended claim 1 by adding step (b): "amplifying exon 2 and exon 3 under conditions suitable to obtain an amplified product." Therefore, the rejection is now believed to be moot.

The Examiner has rejected claims 2-4 under 35 U.S.C. §112, second paragraph, as being "indefinite" for failing to clearly reference the figures. In particular, the Examiner asserts that, "Figure 2 recites multiple sequences and thereby it is unclear as to which intron sequence the claims are referring to." Applicants respectfully disagree.

However to expedite prosecution, Applicants have cancelled claim 2-3 and have amended claim 4 by deleting the reference to figures and by inserting SEQ ID NOs. Therefore, the rejection is now believed to be moot.

The Examiner has rejected claims 5-7 under 35 U.S.C. §112, second paragraph, as being "indefinite" for failing to indicate whether the claims "intend to define the exon which is amplified...or whether the claims only define a primer which may be used if the corresponding exon is amplified." In light of the forgoing amendment to claim 1 step (b) which specifies that the amplification of "exon 2 and exon 3 is under conditions suitable to obtain an amplified product", the forgoing rejection is now believed to be moot.

The Examiner has rejected claims 12 and 15 under 35 U.S.C. §112, second paragraph, as being "indefinite" based on the recitation of "alleles" because it is not clear "whether the primer hybridizes to intron 3 of each of the HLA-A, HLA-B and HLA-C alleles or hybridizes to intron 3 of only one of the HLA-A or HLA-B or HLA-C alleles." Applicants respectfully disagree.

However, in order to expedite prosecution, Applicants have cancelled claim 12 and 15. Therefore the rejection is now believed to be moot.

The Examiner has rejected claim 16 and 17 under 35 U.S.C. §112, second paragraph, as being "indefinite and confusing because the claims improperly depend from 2 claims simultaneously." Applicants respectfully disagree.

However, in order to expedite prosecution, Applicants have cancelled claim 16 and 17. Therefore the rejection is now believed to be moot.

The Examiner has rejected claim 22 under 35 U.S.C. §112, second paragraph, as being "vague...as to whether the claim is intended to be limited to methods of amplifying an HLA-A alleles or methods of typing or subtyping an HLA-A allele." Applicants respectfully disagree.

However to expedite prosecution, Applicants have amended claim 22 to recite a method of typing HLA-A alleles comprising the amplification method as described in claim 1. Therefore the rejection is now believed to be moot.

The Examiner has rejected claim 23-25 under 35 U.S.C. §112, second paragraph, as being "indefinite and confusing over the recitation of "or a line probe assay." In particular, the Examiner is of the opinion that, a claim may not be simultaneously drawn to both a product and a method."

In response, Applicants have cancelled claim 23 and 25 and have amended claim 24 to delete the reference to a "line probe assay." Therefore the rejection is now believed to be moot.

Based on the amendments discussed above, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing 35 U.S.C. § 112, second paragraph, rejections.

Rejection of Claim s 1,5, 6, 10-11, 13, 14, 22, 24 and 25 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1, 5, 6, 10-11, 13, 14, 22, 24 and 25 under 35 U.S.C. §102(e) as being anticipated by Yang (U.S. Patent No.6,030,775; hereafter "Yang"). Applicants respectfully traverse this rejection.

Amended claim 1 is drawn to a method for amplifying exon 2 and exon 3 of HLA-A alleles using **locus-specific primers that** hybridizes with locus-specific target sequences at specified positions within introns 2 and/or 3 of the alleles, and wherein the target position constitute the 3' end of the primer. Exon 2 and 3 are thus amplified **separately** in one reaction.

In contrast, Yang teaches methods for amplifying exon 2 and exon 3 of the HLA-A gene with primers in intron 1 and 3. Exon 2 and exon 3 are therefore amplified together in one reaction. The Examiner points out that in Yang (column 5), "exons 2 and 3 **could**

be amplified individually by selecting a second amplification primer for Exon 2 and a first primer for exon 3 which hybridizes with intron 2." However, this is not exemplified. The Applicants respectfully point out that the primers that **could** be used for the separate amplification of exon 2 and 3 are situated in intron 2 (column 5), as indicated in Figure 3. However, in Figure 3, the possible primers situated in intron 2 are totally spread over intron 2. None of these primers in Figure 3 have their 3' end at the positions indicated in claim 1. Therefore, Yang does not teach or suggest the presently claimed invention.

Moreover, the primers exemplified by Yang are not locus-specific, as claimed by Applicants. Specifically, the first primer indicated on intron 2 of HLA-A (i.e. the primer with sequence GTGAGTGACCCCRGCCS) also amplifies HLA-C (S = G or C). Furthermore, Yang fails to teach or suggest locus-specific target positions within intron 2, whereby the target positions are specifically suitable for the design of locus-specific primers, and whereby the target location is positioned at the 3' end of the primer. Therefore, the primers exemplified by Yang are not locus-specific and the method of amended claim 1 using such locus specific primers is not anticipated by Yang.

Claim 5 is dependent on claim 1 and, thus, for the reasons stated above, is not anticipated by Yang.

Amended claim 10 and new claim 26 are drawn to a primer for the locus-specific amplification of exon 2 or exon 3 of HLA-A alleles characterized in that the primer specifically hybridizes to certain locus-specific target sequences within intron 2 or intron 3, and whereby the target location is positioned at the 3' end of the primer. Yang fails to teach or suggest such primers. Therefore, claims 10 and 26 are not anticipated by Yang.

Amended claim 22 is drawn to a method for typing HLA-A alleles using the amplification method recited in claim 1. As pointed out above, the method of claim 1 is not anticipated by Yang et al. Therefore, the method of typing HLA-A alleles recited in claim 1 also is not anticipated by Yang.

Amended claims 24 and new claim 27 are, respectively, directed to a primer mix and a diagnostic kit containing the primer mix. Yang fails to teach or suggest a primer mix for use in the amplification of exon 2 and 3 of HLA-A alleles, characterized in that the primers specifically hybridize to the certain locus-specific target sequences in intron 2 or 3, and whereby the target location is positioned at the 3' end of the primer. Claim 26

requires that the primer set contain a reverse primer and a reverse or a forward primer which, when used together, are able to specifically amplify exon 2 and 3 of HLA-A alleles without co-amplification of the other Class I alleles. Yang does not teach or suggest such a primer mix, or a diagnostic kit comprising the primer mix. Therefore, claims 24 and 27 are not anticipated by Yang.

While in no way acquiescing to the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have cancelled claims 6, 11, 13, 14, 16 and 25, thereby rendering the rejection under 35 U.S.C § 102(e) against these claims moot.

New claim 28 and claims depending thereon, are directed to a method for amplifying exon 2, exon 3 and exon 4 of HLA-A alleles using primers hybridizing to intron 2 and 3 of HLA-A. Therefore, new claims 28-38 are not anticipated by Yang.

Accordingly, based at least on the above, Applicants respectfully request that the rejections under 35 U.S.C. § 102(e), be withdrawn.

Rejection of Claims 1-8, 10, 11, 13, 14, 22, 22, 24 and 25 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-8, 10, 11, 13, 14, 22, 22, 24 and 25 under 35 U.S.C. §103(a) as being unpatentable over by Yang et al. (U.S. Patent No.6,030,775; hereafter "Yang"). In particular, the Examiner asserts that the generation of additional primers would have been obvious in view of the teaching of the sequence alignment of introns 2 and 3 of HLA-A, HLA-B and HLA-C and the guidance provided by Yang as to how to select additional locus-specific primers. Applicants respectfully traverse this rejection.

Yang fails to teach or suggest, or provide any guidance or motivation whatsoever, regarding how to select for **locus-specific** primers. The only phrase regarding the selection of the primers mentioned by Yang is in column 4, lines 16-19, where the authors state that "it will be advantageous to select primers to avoid variable bases, although in some of the primers discussed, intra-locus variation is taken into account". In addition, Yang teaches the selection of primers within intron 2 of HLA-A that are designed over almost the entire range of the intron 2 sequence (see Figure 3). Therefore,

Yang clearly fails to provide any motivation or reasonable expectation of success for selecting **locus specific primers**.

Moreover, as taught by the Applicants at page 4 of the present specification, "locus-specific primer annealing sites are scarce ..., and separate locus-specific amplification of exon 2, exon 3 and/or exon 4 of HLA-A, HLA-B and HLA-C is not evident". In other words, Applicants have shown that the locus-specific target sequence recited in claim 1 is particularly suitable for designing an efficient primer for the locus-specific amplification of exon 2 and exon 3. From these positions, forward as well as reverse primers can be designed. Indeed, of particular importance in the design of primers is that the target position located at the 3' site of the primer be **locus-specific**, as demonstrated in Tables 1-11 on pages 13-22 of the present specification, and as claimed by the applicants. The locus-specificity is important because the sequences of Class I alleles are very similar.

Furthermore, Yang fails to teach or suggest any locus-specific sites identified and claimed by the Applicants that are particularly suitable for primer design. In fact, Yang fails to teach or suggest any locus-specific primers whatsoever within intron 2. As previously pointed out, the first primer indicated on intron 2 of HLA-A (i.e. the primer with sequence GTGAGTGACCCCRGCCS; Figure 3) taught by Yang will also amplify HLA-C (S = G or C). Moreover, Yang fails to demonstrate that selection of 2 primer pairs will even work for the separate amplification of exon 2 and 3 in one reaction. Indeed, only by way of the present invention was this first demonstrated.

Lastly, in Example 5, under point 5.2, Applicants show that the amplicons obtained by separate amplification of exon 2 and 3 enable a clearer and more pronounced typing than the larger amplicon obtained by amplification of exon 2 and 3 in one single amplicon. This result, namely, that small amplicons are easy to amplify and result in a more efficient hybridization of probes and consequently in a more efficient typing of HLA alleles, was entirely unexpected.

Accordingly, for at least all of the foregoing reasons, Applicants respectfully request that the Examiner reconsider claims 1-8, 10, 11, 13, 14, 22, 24 and 25 and withdraw the forgoing rejection under 35 U.S.C § 103(a).

Rejection of Claims 9, 12, 15 and 23

Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 9, 12, 15 and 23 under 35 U.S.C. §103(a) as being unpatentable over by Yang et al. (U.S. Patent No.6,030,775; hereafter "Yang") in view of Date (Tissue Antigens (1996) 47:93-101; hereafter "Date") and Scheltinga (Human Immunology (1997) 57:120-128; hereafter "Scheltinga"). In particular, the Examiner is of the opinion that it would have been obvious to one skilled in the art to modify the method disclosed by Yang so as to have amplified exon 4 using a primer such as disclosed by Date or Scheltinga. Applicants respectfully traverse this rejection.

At the time of the present invention, a skilled person wanting to additionally amplify exon 4 using the methods disclosed by Yang would have thought to amplify exon 4 together with exon 2 and 3. Yang only demonstrates the amplification of exon 2 and 3 **together** and not separately. Thus, Yang only provided motivation to amplify exon 2 and 3 together, not separately, as claimed by Applicants.

At the time of the present invention, Date and Scheltinga fail to make up for this deficiency in Yang, i.e.) the amplification of the individual exons 2, 3 and 4 in one reaction. Date only discloses two primers that hybridizes to exon 4 in order to amplify exon 4. Date does not disclose any primer in intron 3, much less a locus-specific primer.

Scheltinga also failed to teach or suggest an amplification primer situated in intron 3. The primer taught in intron 3 by Scheltinga is a sequence primer, which is not locus-specific. Scheltinga teaches the amplification of exon 1-5 using amplification primers A5.4 and A3.2 (Figure 1), which is also a large amplicon similar to the teaching disclosed in Yang. Nowhere, does Scheltinga teach or suggest the separate amplification of exon 2, exon 3 and exon 4 in one reaction. Therefore, one skilled in the art would not have been motivated to have used a reverse primer in exon 4 to amplify exon 2, 3, and 4 together in one amplicon, as claimed by the Applicants.

Thirdly, there is no guidance in any of Yang, Date or Scheltinga as how to select for locus-specific amplification primers for the individual amplification of exon 2, 3 and 4 of HLA-A. The only guidance by Scheltinga is on page 121, 2nd column, in the part 'Amplification' where is mentioned that "Specific locus amplification of HLA-A was obtained by using primers A5.4 and degenerate primer A3.2(c/t). This primer pair

amplifies exons 1 to 5". On page 94 of Date, under "PCR primers", it is described that several primers were designed in this study. As seen from Figure 1, primers CGA4S and CGA43S are designed in exon 4 to distinguish A*0201 and A*0207 from A*0215N. Both primers are located in exon 4. Thus, the only purpose of these primers is to distinguish between few specific HLA-A alleles, and not to be used in one amplification reaction together with the amplification of exon 2 and 3 separately, as claimed by the Applicants.

In sum, as discussed above, it would not have been obvious at the time of the present invention, for the skilled artisan to have amplified exon 2, exon 3 and exon 4 separately in one reaction using locus-specific primers located in intron 2 and 3, as presently claimed. In fact, cited references teach away from claimed invention.

In addition, previous claims 12, 15 and 23 have been cancelled and, thus, the rejection is moot as applied to these claims.

Accordingly, for at least the forgoing reasons, Applicants respectfully request the Examiner reconsider and withdraw the forgoing rejection under 35 U.S.C § 103(a).

Rejection of Claims 16 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 16 under 35 U.S.C. §103(a) as being unpatentable over by Yang et al. (U.S. Patent No.6,030,775; hereafter "Yang") in view of Mullis (US Patent No. 4,683,195; hereafter "Mullis").

Applicant is respectfully traversing this rejection. Claim 16 has been cancelled. New claim 27 is directed to a primer mix for use in the amplification of Exon 2 and 3. As discussed above, Yang fails to teach or suggest how to select primers that specifically hybridizes to a locus-specific target sequence within intron 2 and/or 3 of the HLA-A alleles, as claimed by the Applicant. Neither does Mullis teach or suggest such a primer mix. Indeed, the primers of the presently claimed invention have been designed in such a way as to be able to amplify exon 2 and exon 3 of HLA-A alleles only as demonstrated by the working examples provided in the specification. Therefore, new claim 27 is inventive over Yang and Mullis.

Accordingly, Applicant respectfully request the Examiner reconsider and withdraw the forgoing 35 U.S.C § 103(a) rejection.

Rejection of Claims 17 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 17 under 35 U.S.C. §103(a) as being unpatentable over by Yang, Date and Scheltinga in view of Mullis.

While in no way acquiescing to the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have cancelled Claim 17. Therefore, the rejection is now moot.

Moreover as previously discussed, there is no teaching in any of the cited references to individually amplify exon 2, 3 and 4 of HLA-A alleles using a primer mix, as claimed by the applicants. To the contrary, based on the teachings of Yang, Date, Scheltinga and Mullis, one skilled in the art would have been motivated to have amplified exon 2-4 together using a single primer set.

Accordingly, Applicant respectfully request the Examiner reconsider and withdraw the forgoing rejection under 35 U.S.C § 103(a).

Priority Claim

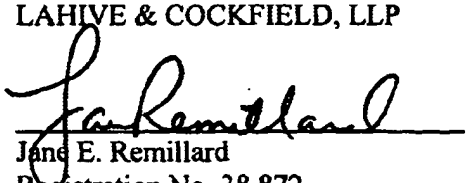
The Examiner has acknowledged Applicants' claim for foreign priority based on an application EP 99870068.6 filed 04/09/99. The Examiner notes, however, that Applicants have not filed a certified copy of the EP application under 35 U.S.C. 119(b). Accordingly, Applicants submit herewith a certified copy of EP 99870068.6.

CONCLUSION

In view of the forgoing, entry of amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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